At page 36 please amend Table 6 to read:

IGP1475(SEQ ID NO: 19)	T	G	S	S	T	G	G	X	Q	G	S	H	H	E								
IGP1477(SEQ ID NO: 20)	E	S	S	R	D	G	S	X	**H**	P	R	S	H	D								
IGP1564(SEQ ID NO: 21)	E	Q	S	A	D	S	S	X	**H**	S	G	S	G	H								
IGP1546(SEQ ID NO: 22)	S	H	Q	C	H	Q	E	S	T	X	G	R	S	R	G	R	C	G	R	S	G	S

Immediately before the claims, please insert the **Sequence Listing** (PatentIn Version 3.0) enclosed herewith.

IN THE CLAIMS:

Please amend claims 3 -22 as follows:

3. (Amended) A peptide according to [claim 1-2] claim 1 characterised in that said peptide is biotinylated.

4. (Amended) A peptide according to [claim 1-3] claim 1 characterised in that said peptide is a synthetic peptide.

5. (Amended) A peptide according to [claim 1-4] claim 1 characterised in that said peptide contains 4 or 6 residues between the cysteine residues.

6. (Amended) A peptide according to [claim 1-5] claim 1 characterised in that said peptide has a sequence containing 14, 15, 16, 17 or 18 amino acids.

7. (Amended) A peptide according to [claim 1-6] claim 1 characterised in that said peptide has one of the following primary amino acid structures:

8 AA – Cysteine – 2 AA – Citrulline – 3 AA – Cysteine – 2 AA (SEQ ID NO: 1) or

5 AA – Cysteine – 2 AA – Citrulline – 3 AA – Cysteine – 2 AA (SEQ ID NO: 2) or

4 AA – Cysteine – 2 AA – Citrulline – 3 AA – Cysteine – 2 AA (SEQ ID NO: 3) or

8 AA – Cysteine – 2 AA – Citrulline – 1 AA – Cysteine – 4 AA (SEQ ID NO: 4) or

6 AA – Cysteine – 2 AA – Citrulline – 1 AA – Cysteine – 4 AA (SEQ ID NO: 5) or
4 AA – Cysteine – 2 AA – Citrulline – 1 AA – Cysteine – 4 AA (SEQ ID NO: 6).

8. (Amended) A peptide according to [claim 1-7] claim 1 characterised in that the amino acids flanking the citrulline residue have a small volume and that they do not interact with the citrulline side chain.

9. (Amended) A peptide according to [claim 1-8] claim 1 comprising the amino acid sequence

QDTIHGHPCSXXGHRCGY (SEQ ID NO: 7), or
QDTIHGHPCSSXGHRCGY (SEQ ID NO: 8), or
QDTIHGHPCSXXGHQCGY (SEQ ID NO: 9), or
QDTIHGHPCSXXGHRCGQ (SEQ ID NO: 10), or
QDTIHGHPCSXXGHQCGQ (SEQ ID NO: 11), or
QDTIHGHPCSXXGCRPGY (SEQ ID NO: 12), or
HGHPCSXXGHRCGY (SEQ ID NO: 13), or
HGHPCSXXGCRPGY (SEQ ID NO: 14), or
HGHGCDXXGHRCGQ (SEQ ID NO: 15), or
HGHGCDSXGHRCGQ (SEQ ID NO: 16), or
QDTIVGWGCDSXGCRPGQ (SEQ ID NO: 17), or
VGWGCDSXGCRPGQ (SEQ ID NO: 18).

10. (Amended) An antibody raised upon immunisation with a peptide according to [any of the claims 1-9] claim 1, with said antibody being specifically reactive with said peptide and with said antibody being preferably a monoclonal antibody.

11. (Amended) An anti-idiotype antibody raised upon immunisation with an antibody according to claim 10, with said anti-idiotype antibody being specifically reactive with the antibody of claim 10, thereby mimicking a peptide according to [claims 1-9] claim 1, and with said antibody being preferably a monoclonal antibody.

12. (Amended) A diagnostic kit for use in detecting auto-immune diseases such as rheumatoid arthritis, said kit comprising at least one peptide according to [any of the claims 1-9] claim 1, or an antibody according to [any of the claims 10 or 11] claim 10, with said peptide or antibody [being possibly] optionally bound to a solid support.

Q9 cont

13. (Amended) A diagnostic kit according to claim 12, said kit comprising a range of peptides according to [any of claims 1-9] claim 1 or of antibodies according to [any of claims 10 or 11] claim 10, [possibly] optionally in combination with antigens that constitute immunogenic determinants for other auto-immune diseases, wherein said peptides are attached to specific locations on a solid substrate.

14. (Amended) A diagnostic kit according to claim [12 or] 13, wherein said solid support is a membrane strip [and said peptides are coupled to the membrane in the form of parallel lines].

15. (Amended) A diagnostic kit according to claim [12 or] 13 wherein certain peptides are not attached to a solid support but are provided in the binding solution to be used as competitors and/or to block other antibodies that are present in sera from patients with autoimmune disease other than rheumatoid arthritis, thereby decreasing or eliminating possible cross-reaction and/or a-specific binding.

16. (Amended) Method for producing a peptide according to [any of the claims 1-9] claim 1, by classical chemical synthesis, wherein citrulline residues are substituted for arginine residues at certain steps during the chemical synthesis.

17. (Amended) Method for producing a peptide according to [claims 1-9] claim 1, wherein the primary amino acid sequence is produced by classical chemical synthesis, and wherein at least one arginine residue subsequently is transformed towards a citrulline residue by contacting said peptide with a peptidylarginine deiminase.

18. (Amended) An immunotoxin molecule comprising a cell recognition molecule being a peptide of [any of the claims 1-9] claim 1, or an antibody according to [claim 10 or 11] claim 10, covalently bound to a toxin molecule or active fragment thereof.

19. (Amended) A medicament comprising a peptide according to [any of the claims 1-9] claim 1 or an antibody according to [any of the claims 10 or 11] claim 10 or an immunotoxin molecule according to claim 18 [or compositions thereof for use as a medicament].

Q9 cont

20. (Amended) A diagnosticum for rheumatoid arthritis comprising [Use of] a peptide according to [claims 1-9] claim 1 or an antibody according to claim 10 [or 11] or an immunotoxin molecule according to claim 18 [or a composition thereof for the preparation of a medicament or of a diagnosticum for rheumatoid arthritis].

21. (Amended) A medicament to treat autoimmune diseases comprising [Use of] a peptide according to claim 1[-9 or a composition thereof for the preparation of a medicament to treat autoimmune diseases by increasing] whereby the size of antigen-immune complexes is increased, thereby improving the clearance of the formed immune complexes.

22. (Amended) A medicament for oral or nasal administration to treat autoimmune disease comprising [Use of] a peptide according to claim 1[-9 or a composition thereof for the preparation of a medicament for oral or nasal administration to treat autoimmune diseases by inducing a state of systemic hyporesponsiveness or tolerance to said peptide of composition].

REMARKS

AMENDMENTS

The specification has been amended to provide SEQ ID NOs for the respective sequences and provide a papercopy of the Sequence Listing in PatentIn Version 3.0. A clean set of the replacement paragraphs is provided herewith.

The claims have been amended to delete recitation of multiple dependency, clarify the claimed subject matter and add SEQ ID NO: references. No new matter has been entered. Claims 1-22 are now pending. A clean set of the pending claims is supplied herewith.

PRIORITY CLAIM

Priority under 35 U.S.C. § 119 is hereby claimed to the following priority document(s), filed in a foreign country within twelve (12) months prior to the filing of the above-referenced United States utility patent application:

Country	Priority Document Appl. No.	Filing Date
EP	99870280.7	21 December 1999
EP	00870195.5	08 September 2000

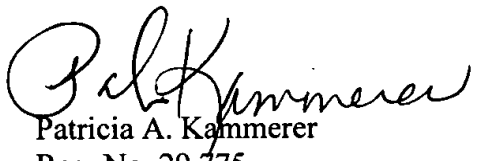
A certified copy of each listed priority document is submitted herewith. Prompt acknowledgment of this claim and submission is respectfully requested.

CONCLUSION

In view of the foregoing amendments, applicants respectfully submit the claims are in proper form and condition for allowance. Applicants request that the claims be allowed and the application advanced to issue.

The Examiner is invited to contact the undersigned attorney at (713) 787-1438 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,



Patricia A. Kammerer
Reg. No. 29,775
Attorney for Assignee
INNOGENETICS N.V.

HOWREY SIMON ARNOLD & WHITE, LLP
750 Bering Drive
Houston, TX 77057–2198
Tel: (713) 787-1400
Fax: (713) 787-1440

Date: March 26, 2001

CLAIMS PENDING FOLLOWING PRELIMINARY AMENDMENT

1. A peptide comprising a sequence of less than 50 amino acids characterised in that
   - it contains a peptide turn comprising at least one citrulline residue, and
   - it contains less than 12 amino acids between two cysteine residues, with said citrulline residue being one of the amino acids between said cysteine residues and
   - said peptide is specifically recognised by autoimmune antibodies from patients suffering from rheumatoid arthritis.

2. A peptide according to claim 1 characterised in that said peptide is a cyclic peptide.

3. (Amended) A peptide according to claim 1 characterised in that said peptide is biotinylated.

4. (Amended) A peptide according to claim 1 characterised in that said peptide is a synthetic peptide.

5. (Amended) A peptide according to claim 1 characterised in that said peptide contains 4 or 6 residues between the cysteine residues.

6. (Amended) A peptide according to claim 1 characterised in that said peptide has a sequence containing 14, 15, 16, 17 or 18 amino acids.

7. (Amended) A peptide according to claim 1 characterised in that said peptide has one of the following primary amino acid structures:

8 AA – Cysteine – 2 AA – Citrulline – 3 AA – Cysteine – 2 AA (SEQ ID NO.1), or

5 AA – Cysteine – 2 AA – Citrulline – 3 AA – Cysteine – 2 AA (SEQ ID NO. 2), or

4 AA – Cysteine – 2 AA – Citrulline – 3 AA – Cysteine – 2 AA (SEQ ID NO. 3), or

8 AA – Cysteine – 2 AA – Citrulline – 1 AA – Cysteine – 4 AA (SEQ ID NO. 4), or

6 AA – Cysteine – 2 AA – Citrulline – 1 AA – Cysteine – 4 AA (SEQ ID NO. 5), or

4 AA – Cysteine – 2 AA – Citrulline – 1 AA – Cysteine – 4 AA (SEQ ID NO. 6).

8. (Amended) A peptide according to claim 1 characterised in that the amino acids flanking the citrulline residue have a small volume and that they do not interact with the citrulline side chain.

9. (Amended) A peptide according to claim 1 comprising the amino acid sequence

QDTIHGHPCSXXGHRCGY (SEQ ID NO. 7), or
QDTIHGHPCSSXGHRCGY (SEQ ID NO. 8), or
QDTIHGHPCSXXGHQCGY (SEQ ID NO. 9), or
QDTIHGHPCSXXGHRCGQ (SEQ ID NO. 10), or
QDTIHGHPCSXXGHQCGQ (SEQ ID NO. 11), or
QDTIHGHPCSXXGCRPGY (SEQ ID NO. 12), or
HGHPCSXXGHRCGY (SEQ ID NO. 13), or
HGHPCSXXGCRPGY (SEQ ID NO. 14), or
HGHGCDXXGHRCGQ (SEQ ID NO. 15), or
HGHGCDSXGHRCGQ (SEQ ID NO. 16), or
QDTIVGWGCDSXGCRPGQ (SEQ ID NO. 17), or
VGWGCDSXGCRPGQ (SEQ ID NO. 18).

10. (Amended) An antibody raised upon immunisation with a peptide according to claim 1, with said antibody being specifically reactive with said peptide and with said antibody being preferably a monoclonal antibody.

11. (Amended) An anti-idiotype antibody raised upon immunisation with an antibody according to claim 10, with said anti-idiotype antibody being specifically reactive with the antibody of claim 10, thereby mimicking a peptide according to claim 1, and with said antibody being preferably a monoclonal antibody.

12. (Amended) A diagnostic kit for use in detecting auto-immune diseases such as rheumatoid arthritis, said kit comprising at least one peptide according to claim 1, or an antibody according to claim 10, with said peptide or antibody optionally bound to a solid support.

13. (Amended) A diagnostic kit according to claim 12, said kit comprising a range of peptides according to claim 1 or of antibodies according to claim 10, optionally in combination with antigens that constitute immunogenic determinants for other auto-immune diseases, wherein said peptides are attached to specific locations on a solid substrate.

14. (Amended) A diagnostic kit according to claim 13, wherein said solid support is a membrane strip.

15. (Amended) A diagnostic kit according to claim 13 wherein certain peptides are not attached to a solid support but are provided in the binding solution to be used as competitors and/or to block other antibodies that are present in sera from patients with autoimmune disease other than rheumatoid arthritis, thereby decreasing or eliminating possible cross-reaction and/or a-specific binding.

16. (Amended) Method for producing a peptide according to claim 1, by classical chemical synthesis, wherein citrulline residues are substituted for arginine residues at certain steps during the chemical synthesis.

17. (Amended) Method for producing a peptide according to claim 1, wherein the primary amino acid sequence is produced by classical chemical synthesis, and wherein at least one arginine residue subsequently is transformed towards a citrulline residue by contacting said peptide with a peptidylarginine deiminase.

18. (Amended) An immunotoxin molecule comprising a cell recognition molecule being a peptide of claim 1, or an antibody according to claim 10, covalently bound to a toxin molecule or active fragment thereof.

19. (Amended) A medicament comprising a peptide according to claim 1 or an antibody according to claim 10 or an immunotoxin molecule according to claim 18.

20. (Amended) A diagnosticum for rheumatoid arthritis comprising a peptide according to claim 1 or an antibody according to claim 10 or an immunotoxin molecule according to claim 18.

21. (Amended) A medicament to treat autoimmune diseases comprising a peptide according to claim 1 whereby the size of antigen-immune complexes is increased, thereby improving the clearance of the formed immune complexes.

22. (Amended) A medicament for oral or nasal administration to treat autoimmune disease comprising a peptide according to claim 1.

REPLACEMENT PARAGRAPHS

At page 2, line 1, please insert a new paragraph to read:

This application claims priority to EP 99870280.7 filed 21 December 1999 and EP 00870195.5 filed 08 September 2000.

At page 6 spanning 7, please replace the final paragraph to read:

Fig. 4: Comparison between LIA using synthetic peptides of the present invention (= Fg LIA), Western Blot with natural filaggrin (= Fg Blot) and the APF fluorescence test using human buccal cells (APF test) for the detection of RA specific autoantibodies. 412 human sera are tested: 153 disease controls (1), 47 sera from patients with early disease (less than 12 months of symptoms) (2) and 212 longstanding RA sera (more than 4 years of symptoms) (3).

At page 10, please replace the paragraph spanning lines 17 - 26 to read:

In a more specific embodiment the present invention relates to peptides described above characterised in that they have one of the following primary amino acid structures:

8 AA – Cysteine – 2 AA – Citrulline – 3 AA – Cysteine – 2 AA (SEQ ID NO: 1) or

5 AA – Cysteine – 2 AA – Citrulline – 3 AA – Cysteine – 2 AA (SEQ ID NO: 2) or

4 AA – Cysteine – 2 AA – Citrulline – 3 AA – Cysteine – 2 AA (SEQ ID NO: 3) or

8 AA – Cysteine – 2 AA – Citrulline – 1 AA – Cysteine – 4 AA (SEQ ID NO: 4) or

6 AA – Cysteine – 2 AA – Citrulline – 1 AA – Cysteine – 4 AA (SEQ ID NO: 5) or

4 AA – Cysteine – 2 AA – Citrulline – 1 AA – Cysteine – 4 AA (SEQ ID NO: 6).

At page 12, please replace Table 1 to read:

Position	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
IGP1611 (SEQ ID NO: 7)	Q	D	T	I	H	G	H	P	C	S	X	X	G	H	R	C	G	Y
IGP1646(SEQ ID NO: 8)	Q	D	T	I	H	G	H	P	C	S	S	X	G	H	R	C	G	Y
IGP1647(SEQ ID NO: 9)	Q	D	T	I	H	G	H	P	C	S	X	X	G	H	Q	C	G	Y
IGP1648(SEQ ID NO: 10)	Q	D	T	I	H	G	H	P	C	S	X	X	G	H	R	C	G	Q
IGP1649(SEQ ID NO: 11)	Q	D	T	I	H	G	H	P	C	S	X	X	G	H	Q	C	G	Q
IGP1650(SEQ ID NO: 12)	Q	D	T	I	H	G	H	P	C	S	X	X	G	C	R	P	G	Y
IGP1651(SEQ ID NO: 13)					H	G	H	P	C	S	X	X	G	H	R	C	G	Y
IGP1676(SEQ ID NO: 14)					H	G	H	P	C	S	X	X	G	C	R	P	G	Y
IGP1687(SEQ ID NO: 15)					H	G	H	G	C	D	X	X	G	H	R	C	G	Q
IGP1684(SEQ ID NO: 16)					H	G	H	G	C	D	S	X	G	H	R	C	G	Q
IGP1685(SEQ ID NO: 17)	Q	D	T	I	V	G	W	G	C	D	S	X	G	C	R	P	G	Q
IGP1686(SEQ ID NO: 18)					V	G	W	G	C	D	S	X	G	C	R	P	G	Q

At page 14 spanning page 15, please replace the final paragraph to read:

Further analysis of the different peptide structures described above revealed additional specific interactions between residues, which are a prerequisite for immunoreaction of the designed peptides with autoantibodies present in sera from patients suffering from rheumatoid arthritis. This can be described as follows:

a) Type I peptides: Cys – six residues – Cys:

8 AA – Cysteine – 2 AA – Citrulline – 3 AA – Cysteine – 2 AA (SEQ ID NO: 1) or

5 AA – Cysteine – 2 AA – Citrulline – 3 AA – Cysteine – 2 AA (SEQ ID NO: 2) or

4 AA – Cysteine – 2 AA – Citrulline – 3 AA – Cysteine – 2 AA (SEQ ID NO: 3).

At page 17, lines 12 - 16, please replace the paragraph to read:

b) Type II peptides: Cys – four residues – Cys peptides:

8 AA – Cysteine – 2 AA – Citrulline – 1 AA – Cysteine – 4 AA (SEQ ID NO: 4) or

6 AA – Cysteine – 2 AA – Citrulline – 1 AA – Cysteine – 4 AA (SEQ ID NO: 5) or

4 AA – Cysteine – 2 AA – Citrulline – 1 AA – Cysteine – 4 AA (SEQ ID NO: 6).

At page 31 spanning page 32, please replace Table 4 to read:

IGP1611 (SEQ ID NO: 7)	Q	D	T	I	H	G	H	P	C	S	X	X	G	H	R	C	G	Y
IGP1646(SEQ ID NO: 8)	Q	D	T	I	H	G	H	P	C	S	S	X	G	H	R	C	G	Y
IGP1647(SEQ ID NO: 9)	Q	D	T	I	H	G	H	P	C	S	X	X	G	H	Q	C	G	Y
IGP1648(SEQ ID NO: 10)	Q	D	T	I	H	G	H	P	C	S	X	X	G	H	R	C	G	Q
IGP1649(SEQ ID NO: 11)	Q	D	T	I	H	G	H	P	C	S	X	X	G	H	Q	C	G	Q
IGP1650(SEQ ID NO: 12)	Q	D	T	I	H	G	H	P	C	S	X	X	G	C	R	P	G	Y
IGP1651(SEQ ID NO: 13)					H	G	H	P	C	S	X	X	G	H	R	C	G	Y
IGP1676(SEQ ID NO: 14)					H	G	H	P	C	S	X	X	G	C	R	P	G	Y
IGP1687(SEQ ID NO: 15)					H	G	H	G	C	D	X	X	G	H	R	C	G	Q
IGP1684(SEQ ID NO: 16)					H	G	H	G	C	D	S	X	G	H	R	C	G	Q
IGP1685(SEQ ID NO: 17)	Q	D	T	I	V	G	W	G	C	D	S	X	G	C	R	P	G	Q
IGP1686(SEQ ID NO: 18)					V	G	W	G	C	D	S	X	G	C	R	P	G	Q

At page 36 please replace Table 6 to read:

IGP1475(SEQ ID NO: 19)	T	G	S	S	T	G	G	X	Q	G	S	H	H	E								
IGP1477(SEQ ID NO: 20)	E	S	S	R	D	G	S	X	**H**	P	R	S	H	D								
IGP1564(SEQ ID NO: 21)	E	Q	S	A	D	S	S	X	**H**	S	G	S	G	H								
IGP1546(SEQ ID NO: 22)	S	H	Q	C	H	Q	E	S	T	X	G	R	S	R	G	R	C	G	R	S	G	S